10. (Previously presented) The method of claim 6 wherein the compound is an antibody or antibody fragment immunoreactive with Mac-1 (CD11b/CD18).

11. (Original) The method of claim 1 wherein the compound is administered to a patient in need thereof prior to vascular intervention.

12. (Original) The method of claim 11 wherein the compound is administered to a the patient prior to and after vascular intervention, until healing has occurred.

13. to 17. (Cancelled)

Remarks

Title

The title of this application is the Modulation of Vascular Healing by Inhibition of Leukocyte Adhesion and Function. The title is believed to be fully description of the invention as claimed. Claim 1 is drawn to:

A method of inhibiting or reducing stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:

administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin -mediated adhesion or function, ...

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Abstract

The abstract has been reviewed and is believed to accurately and concisely describe the claimed method. However, it has been shortened to 150 words.

Clarification of Terms

The Board of Appeals has made the following of record (see Paper No. 38).

A) Taber's Cyclopedic Medical Dictionary, 18th Ed., pp130, 166 and 1828 (1997) (892: of record) sets forth the following definitions.

Stenosis: The constriction or narrowing of a passage or orifice.

Aortic Stenosis: Narrowing of the aorta or its orifice due to lesion of the wall with scar formation.

Restenosis: The Recurrence of a stenotic condition as in a heart valve or vessel.

In response to the Board's request (page 3 of Paper No. 38), Applicants clarify their use of the terms "stenosis", restenosis" and "dependent restenosis" as follows.

Stenosis: Narrowing of a blood vessel for the first time. If a vein is transplanted in bypass surgery, it will be subject to stenosis because it will be the first time the transplanted vessel is narrowed. Claim 1 has been amended to incorporate the language of dependent claim 3 to further modify the claimed reference to stenosis.

Restenosis: Re-narrowing of a vessel after mechanical intervention for example with balloon, stent, atherectomy or laser.

Dependent restenosis has been removed from the claims.

Accelerated arteriopathies: Restenosis as well as stenosis (narrowing of vessel) of vein graft or stenosis following transplantation. Accelerated arteriopathies normally develop within months to a year and result in neointimal thickening. Conversely, atherosclerosis-mediated stenosis takes decades to develop.

The claims are directed to a method of inhibiting or reducing accelerated arteriopathies, specifically, (1) stenosis arising from coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs or (2) restenosis of a blood vessel following injury to a vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, by administering a compound which specifically inhibits or reduces leukocyte integrin mediated adhesion or function in an effective amount to inhibit or reduce the accelerated artieriopathies of a blood vessel following injury to vascular tissue. The patient can be either human or animal model as the claims read on either. The reduction or inhibition of stenosis or restenosis can be a reduction or inhibition of narrowing of the blood vessel due to leukocyte integrin-mediated cell adhesion. An effective amount of an anti Mac-1 antibody is determined by routine experimentation by one of skill in the art using information known to those skilled in the art from the administration of other antibodies, the dosages used in the examples for treatment of appropriate animal models, and ultimately, clinical studies to determine the optimal amount. Exemplary amounts are described on page 21, lines 4-16 as ranging between 0.25 mg/Kg to 1 mg/Kg.

One very important concept to recognize is the difference between accelerated arteriopathies such as restenosis and ischemic-reperfusion injury. The following table shows the differences between these two types of disorders.

Disorder	Ischemia-Reperfusion	Restenosis/Accelerated Arteriopathy
Cessation in blood flow?	Yes	No
Endothelium present?	Yes	No
Concern over target organ damage?	Yes	No

Ischemia-Reperfusion and Restenosis are very different disorders with different mechanisms and characteristics. This difference is discussed below with respect to the prior art.

The comment about "whether there is a manipulative difference" at the top of page 3, makes no sense - it appears the examiner is asking if there is a difference between the claimed procedures and the claimed method. Please clarify if this is still an issue.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

a. The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the

claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g.*, Genentech, Inc. v. Novo Nordisk A/S, 108 F3d at 165, 42 USPQ2d at 1004 (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also In re Fisher, 427 F.2d at 839, 166 USPQ at 24; United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (M.I.T. v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation

is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Id. at § 2164.05 (emphasis added).

The patent examiner cannot just assert that the application is not enabled. As stated in In re Marzocchi at 439 F.2d 220 (CCPA 1971:

[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made [, enablement under § 112, first paragraph], to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the Appellant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Id. at 224.

The MPEP instructs examiners to make specific findings of *facts* to rebut Applicants' presumption and ***"specifically identify what information is missing and why one of skill in the art could not supply the information without undue experimentation."*** MPEP at § 2164.05. The examiner should provide references to support a *prima facie* case of lack of enablement. *Id.*

With regard to post-filing art, the CAFC stated in In re Brana, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995), that a post-filing date declaration setting forth test results substantiating utility "pertains to the accuracy of a statement already in the specification. . . . It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed." An important distinction has been made by the Courts between evidence of the knowledge and ability of those of skill in the art at the time of filing and evidence to prove that statements made in the application are correct. In the former case, of course, only evidence which existed prior to the filing of the application, or evidence that certain knowledge existed at

the time of filing, is admissible (In re Hogan, 194 USPQ 527 (CCPA 1977)). In the latter case, any evidence, developed at any time, may be submitted for consideration.

The clearest affirmation of the seasonability of factual evidence developed after the filing date of an application is provided by the Court in In re Marzocchi (169 USPQ 367, 370 (CCPA 1971)). In discussing rejections under 35 USC 112 where an examiner asserts that the unpredictability of the art creates a reasonable doubt as to the accuracy of a particular broad statement (in the application) supporting enablement, the Court states:

Most often, additional factors, such as the teachings of pertinent references[*], will be available to substantiate any doubts that the asserted scope of enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof.

***

Not necessarily *prior* art references, it should be noted, since the question would be regarding the *accuracy* of a statement in the specification, not whether that statement had been made before. [emphasis in the original]

Id. at 367

In *In re Wilson* (135 USPQ 442, 444 (CCPA 1962)), the Court agreed that a reference, published after the filing date of the application, was properly cited to show a state of fact. In *In re Langer* (183 USPQ 288, 297 (CCPA 1974)), the Court again noted that later published

references "are properly cited for the purpose of showing a fact." In *In re Rainer* (134 USPQ 343, 345 (CCPA 1962)) the Court found no error in the limited use made of a reference published after Appellant's filing date to show a fact. While all of these cases involved publications cited by the Patent Office in support of rejections, the same standard applies to evidence cited by Appellant. See In re Hogan.

Each piece of post-filing art may be evidence of the enablement of one or more element in the claims. Each piece goes to the issue of enablement of the claimed invention as a whole. The post filing art need only display the proposition for which it is submitted. It is not necessary, nor is it required, that each element of the claimed invention be within a single post filing art reference. Each fact and piece of evidence supporting enablement can and should be considered for what it shows. It is improper to require one specific form of evidence while ignoring others. It is the evidence as a whole that must be considered. Elements of the claimed invention *independently* described in the post filing art, can cumulatively demonstrate the feasibility of reducing the invention to practice using materials and methods described in the specification and/or known by a skilled artisan as of the time of filing.

Lastly, there is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. MPEP at § 2164.02, *citing* Gould v. Quigg, 822 F.2d 1074 (Fed. Cir. 1987). "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id.*

Amgen, Inc., v. Hoechst Marion Roussel Inc., 314 F.3d 1313 ,65 USPQ2d 1385 (Fed. Cir 2003) held that the standard for enablement is two-fold: 1. "where the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed"; 2. "the specification need teach only one mode of making and using a claimed composition." *Id.* at 1329. *Amgen* further held that post-filing publications could show enablement in an unpredictable area or art. *Citing Gould v. Quigg*, 822 F.2d 1074, 3 USPQ2d 1302 (Fed. Cir. 1987).

b. The Application contains supporting data and Additional data has been provided

Data has been submitted in the application and subsequently showing the efficacy of one of these inhibitors, antibodies to Mac-1, in appropriate animals for prevention of restenosis. Subsequent studies have shown efficacy in human studies. See the examples at pages 22-23 of the application as filed, using an antibody to Mac-1 to inhibit restenosis following vascular injury. This antibody has also been tested in a phase I clinical trial by Millenium Pharmaceuticals and Xoma, in 2003.

An abstract published in Circulation, Supp. 1, vol. 100, no. 18 November 2, 1999, number 1742, has also been submitted demonstrating that an equivalent effect can be obtained with a peptide inhibitor.

This is in addition to the lengthy discussion in the application as originally filed which defines the integrins and ligands (page 7, lines 13-25; page 8, line 7 to page 9, line 10; page 9, line

22-page 10, line 11); the classes of compounds, including antibodies (page 9, lines 11-22; page 10, line 10-page 11, line 19); peptides and peptidomimetics (page 11, line 20, to page 13, line 19); methods for screening for compounds and generation of synthetic compounds randomly and by computer aided design (page 13, line 20 to page 16, line 15), and nucleic acid molecules (page 16, line 16, to page 19, last line). Carrier materials are dscribed on page 20. Methods for administration are detailed at page 20, line 22, to page 22, line 2.

The efficacy of both the peptide and the antibody demonstrate that ***it is the target selectively bound by the claimed molecule that is critical; not the form of the compound per se.*** Subsequent studies using small molecule inhibitors selectively binding to the same target have also shown the same degree of efficacy.

Accordingly, applicants, by virtue of identifying the critical target, as well as the recognition that not just one but any of several compounds could be effective, have enabled one of skill in the art to practice the claimed method.

c. The Examiner has provided only allegations and references relating to ***clinical efficacy;*** *not support for his rejections using the proper legal standard under 35 U.S.C. 112.*

No proper *prima facie* case for lack of enablement has been established. The Examiner has provided no evidence or convincing argument that the claimed method cannot be used for the *in vivo* purposes described in the specification. Rather, the Examiner has merely expressed the opinion that the claimed method is unpredictable, and cited to references that relate to clinical

optimization, not the legal standard under 35 U.S.C. 112. This clearly does not meet the standard to establish a *prima facie* case of lack of enablement.

The examiner argues that the animal model studies in general relating to restenosis have not correlated well with clinical trial results in human patients, and that this in combination with the breadth of the claims to any compounds which would inhibit or reduce leukocyte-integrin-mediated adhesion, would mean that undue experimentation would be required to practice the claimed method. For some reason the examiner discusses the need for *in vivo* data to demonstrate that a therapy will be effective, but ignores the fact that the examples in the application as originally filed are in fact *in vivo* (although a rabbit rather than a human). There is also discussion about the fact that it takes years of development to prove a clinical treatment. The truth of this is indisputable but not relevant: the fact is that the applicants have provided *in vivo* evidence in their application showing that an antibody to at least one of the claimed integrins was effective in an animal model and in combination with independent third parties have provided evidence that another completely different kind of molecule, a peptide, derived from the integrin ligand glycolipid-anchored urokinase receptor, was also effective. The examiner also focuses on arguments that one could not predict that the compounds could be used in a patient (see for example page 11 of the office action), again ignoring that the same considerations are equally applicable in an animal model and that the success of the treatments in the animal models is proof that these are not valid concerns.

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1. Animal Models are Predictive of Efficacy

The rejection is initially based on the proposition that the animal models, specifically the rat and rabbit animal models used by applicants, do not correlate well with *in vivo* clinical trial results. Enclosed in response were three papers and abstracts of two others. The abstract of Coats, et al., "Remodeling and restenosis: insights from animal studies" Semin. Interv. Cardiol. 2(3), 153-158 (1997), notes that animal studies in remodeling and its contribution to restenosis have been critical, and correlated with human studies. Farb., et al., "Pathology and Chronic Coronary Stenting in Humans," Circulation, 99:44-52 (1999), paper notes at page 51, col. 2, that "These data in the pig model regarding inflammation and thrombus closely reflect the findings observed in human coronary stenting early after implantation (with a relatively longer duration of healing in humans)." The authors then note that there is a difference in the type of vascular injury in normal arteries of animals as compared to the response in human atherosclerotic arteries. (This may be one reason why there has been variable correlation with some reported models). Komatsu, et al., "Neointimal Tissue Response at Sites of Coronary Stenting in Humans" Circulation 98, 224-233 (1998), reports that animal models are generally predictive (page 230), with dogs being an exception (page 232). Kearney, et al., "Histopathology of In-Stent Restenosis in Patients with Peripheral Artery Disease", Circulation, 95:1998-2002 (1997) correlates results in humans obtained at autopsy with animal studies, beginning at the bottom of page 1999, col. 2. The abstract of Folts, et al., J. Am. Coll. Cardio. 33(2), 295-303 (1999), notes

that an animal model, the cyclic flow model of coronary thrombosis, has been useful in predicting which agents are likely to be of benefit in clinical trials.

In summary, the literature supports the use of animal models as predictive of efficacy.

2. Data demonstrates Efficacy of Inhibiting Integrin-mediated Inhibition

Example 2, beginning on page 22 of the application, shows administration of an antibody to rabbits after arterial injury. The data demonstrated that there was a reduction in neointimal area after deep injury of nearly 40% relative to controls. This data alone indicates that the active agent can be effectively delivered. No adverse effects were noted.

Also provided to the examiner was an article by the inventors and others which was submitted to the J. Clin. Invest. entitled "Decreased neointimal formation in Mac-1 (-/-) mice reveals a role for inflammation in vascular repair after angioplasty. (published by Simon, et al., J. Clin. Invest. 105(3), 293-300 (February 2000)). This paper describes the role of inflammation in mechanical arterial injury, in particular Mac-1, which when absent results in significantly less intimal proliferation and thickening after injury.

3. There are numerous protein therapies

The relevance of the comments regarding potential degradation of compound, etc. at pages 11 of the office action is not clear, and indeed, is rebutted by the examples. Many pharmaceutical proteins and numerous antibodies are administered to patients as therapeutics, absent side effects, and without loss of function. For example, as shown by the abstract by Topol, et al., "Long-term protection from myocardial ischemic events in a randomized trial of

brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication" JAMA 278(6):479-484 (1997).

In response to the arguments at page 14, the examiner's attention is drawn to the claim limitation regarding "selectively" binding. This feature alone distinguishes heparin and anti-CD18 antibodies that are reactive with multiple targets. These are also excluded by the functional limitation in claim 1, "administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin -mediated adhesion or function, "

In summary, the claims are enabled by the specification and materials known to those skilled in the art, as required under 35 U.S.C. 112.

Rejection Under 35 U.S.C. § 112, first paragraph (written description)

Claims 1-6, 8, 11 and 12 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection.

a. The Legal Standard

Enzo Biochem, Inc., v. Gen-Probe Incorporated,, 323 F.3d 956 (Fed. Cir. 2002) held that the written description requirement of §112 is met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...i.e., complete or partial

structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 956.

The standard for determining compliance with the written description requirement is an objective standard. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). The court in *Vas-Cath* stated that the applicant's description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed. *Id.* at 1563. An applicant is able to show possession of the claimed invention by "describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565 (Cal. 1997). The scope of the disclosure with which the claims of a specification need in order to meet the written description requirement is not entirely encompassing and thus can be broad in breadth. Generally, a specification may contain a written description of a broadly claimed invention without describing all species that claim encompasses. *Utter v. Hiraga et al.*, 845 F.2d 993 (Fed. Cir. 1988).

A broader interpretation of the written description requirement relating to biotechnology inventions resulted from *Enzo Biochem, Inc., v. Gen-Probe Incorporated*, 323 F.3d 956 (Fed. Cir. 2002), discussed below. The court found that it was "not correct ...that all functional descriptions of genetic material fail to meet the written description requirement." *Id.* at 959. Therefore, the disclosure of the sequence was not always necessary and other types of

disclosures could be examined on a case by case basis. The *Enzo* court adopted provisions from the MPEP's guidelines that allow the written description requirement to be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

Amgen, Inc., v. Hoechst Marion Roussel Inc., 314 F.3d 1313 (Fed. Cir. 2003), also applied the broad interpretation of the written description requirement set out in *Enzo* regarding the type of disclosures that comply with this requirement. *Amgen* deals with an infringement action over plaintiffs' patents to erythropoietin (EPO), process for producing EPO, and cells for producing EPO. The defendants claimed that Amgen failed to sufficiently describe all vertebrate and mammalian cells as engineered in the claimed invention and relied on *Eli Lilly*. The court stated that *Enzo* clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement. Rather, "the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *See Enzo* at 1324. The Court in *Amgen* also distinguished both *Eli Lilly* and *Enzo* because the claim terms at issue "are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO." *Id.*

b. The Claims Meet the Written Description Requirement

The specification supports the use of any "compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function". Detailed description is provided for compounds such as antibodies or antibody fragments (p9-11), peptide and peptidomimetic compounds (p11-p13) and nucleic acid regulators (p16-19) that inhibit or reduce leukocyte integrin-mediated adhesion or function. These compounds share the common feature that they all bind the specifically recited integrins or their ligands. One of skill in the art would be aware of these compounds, many of which are known, and the mechanisms by which they act on the integrins. The Examples of the specification describe in clear detail how one would use a "compound" (in this case anti-Mac-1) to reduce or inhibit leukocyte integrin-mediated adhesion or function. Additional information is provided with respect to the other compounds, and methods of use thereof, as described above with reference to enablement.

The test under written description should not be confused with enablement. The test is only whether there is sufficient evidence the inventors had conceived of the claimed subject matter. There can be no doubt that the specification provides ample evidence of conception of the claimed method, as well as the understanding of the mechanism of action that allows one skilled in the art to substitute any one of a number of other compounds having the same mechanism of action. As in *Amgen*, applicants are not claiming the compounds *per se*, but rather the method of use thereof.

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Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

a. The Legal Standard

Exxon Research and Engineering Company v. United States, 265 F.3d 1371 (Fed. Cir. 2001), stated the standard to be as follows: "If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2." *Id. citing Miles Labs, Inc., v. Shandon, Inc.*, 997 F.2d 870 (Fed. Cir. 1994).

The court further stated that claims do not have to be plain on their face to be definite. Rather, "the claims need be amenable to construction, however difficult that task may be. If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id.*

In *Genzyme corporation v. Transkaryotic Therapies, Inc.*, 346 F.3d 1094 (Fed. Cir. 2003), the court held that in order to discern a term's usage within a claim, one must apply the ordinary and accustomed meaning of the words amongst artisans of ordinary skill in the relevant art at the time of invention. *Id.* Further, the application may consistently and clearly use a term in a manner "either more or less expansive than its general usage in the relevant community, and thus expand or limit the scope of the term in the context of the patent claims." *Id.*

Furthermore, "if the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." *Bausch & Lomb, Inc., v. Alcon Laboratories, Inc.*, 79 F.Supp 243 (W.D. NY 1999),. at 245 citing *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613 (Fed. Cir. 1985).

b. The Claims are Definite

The claims are directed to a method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel by administering an effective amount of a compound that ***specifically*** inhibits or reduces leukocyte integrin-mediated adhesion or function thereby reducing stenosis or restenosis of a blood vessel after injury to vascular tissue. The definitions of the claim terms is discussed above. These are standard definitions that one skilled in the art would be familiar with and have no difficulty in understanding. The method by which stenosis/restenosis is reduced is by inhibiting or reducing integrin-mediated leukocyte adhesion. This is defined in the specification on page 6, lines 13-23. The specific endpoint is to reduce leukocyte integrin-mediated adhesion or function.

An effective amount of compound to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to a vascular tissue is also defined in the specification on pages 20 and 21 of the specification.

The terms stenosis, restenosis have been defined previously in this response. Although the review article by Anderson (1993) describes numerous characteristics of restenosis, the

features of restenosis are defined in the specification on pages 6 and 7. The key parameter that is encompassed in the disorders listed in claim 3 is the specific inhibition or reduction of leukocyte integrin-mediated adhesion. The role of leukocyte adhesion is disclosed in both human and animal models (page 3, lines 4-24 of the specification citing Inoue et al JACC 28(5):1127-1133.)

A common feature between the disorders listed in claim 3 is integrin-mediated leukocyte adhesion. Administering a compound specifically inhibit/reduce integrin binding as defined will be effective in reducing stenosis and restenosis. The effective amount can be routinely titrated for each patient depending on the compound and route of administration regardless of the disorder in order to achieve therapeutic efficacy. This is described in the specification on page 21, lines 4-16.

While Fattori (2003) states that the mechanisms of restenosis differ between balloon and in-stent catheter injuries, both models share the common feature of leukocyte integrin-mediated adhesion, although to different degrees. Balloon catheter injury causes greater cell adherence than in-stent injury. This is supported by the specification in Example 2 that shows that specific blocking of integrin binding causes a 75% reduction in the balloon injured vessel but only a 40% reduction in the in-stent injured vessel. Although still significant, the decreased effect in in-stent injured vessels is a reflection of the reduced contribution of leukocyte adhesion in in-stent restenosis.

Claims 5 and 6 (and withdrawn claims 7 and 9) are quite clear as to what the target is. The claims define a method of administering a compound that reduces leukocyte integrin-

mediated adhesion and function by specifically interfering with either the integrin or the integrin-ligand. The specification teaches very clearly that by blocking interaction of integrins and their ligands one can inhibit leukocyte adhesion and neointima formation, thereby reducing restenosis (page 7, lines 7-12). Therefore a compound that interferes with either the integrin or the integrin receptor will impede the binding occurrence that results in cell adhesion and restenosis. For further clarification the term "their ligands" has been amended to "integrin ligands".

Rejection Under 35 U.S.C. § 102

Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by Genetta et al., *Ann Pharmacol* 30, 251-257 (1996), "as evidenced by" Schwarz et al., *Thromb Res* 107, 121-128(2002), Bendeck et al,. *J Vasc Res* 38,590-599 (2001), Wu et al., *Thromb Res* 101, 127-138 (2001) and ERASER Investigators, *Circulation* 100, 799-806 (1999). Applicants respectfully traverse this rejection.

a. The Legal Standard

The Board cited in their decision on page 7, *Celeritas Tech. ltd v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522 (Fed. Cir. 1998). "It is well settled that a claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." It must be established that a prior art reference discloses each and every element of the claims for a rejection of claims to be properly founded under 35 USC §102. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987);

Scripps Clinic & Research Found v Genentech Inc, 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 927 F.2d 1576:

"Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." (Emphasis added)

"A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation."

"[A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference." *Id at 1576*

b. The Prior Art

Genetta

Genetta discloses results of clinical trials using abciximab to reduce the incidence of abrupt closure and restenosis associated with PTCA. Abciximab was administered by bolus injection prior to and after angioplasty.

Schwarz, Bendeck, Wu and ERASER Investigations

Schwarz was cited to show that abciximab binds to Mac-1. However, it is very clear based on the findings of Mickelson et al. (JACC 1999; 33(1):97-106, for example page 101, 1st column) that abciximab does not bind directly to Mac-1. The actions of abciximab on Mac-1 are indirect and therefore do not "specifically" inhibit or reduce leukocyte integrin-mediated adhesion. Bendeck and Wu were cited to show that abciximab can reduce smooth muscle cell migration following vascular injury. Merely reducing smooth muscle cell migration does not prevent restenosis or stenosis.

The ERASER study was cited to establish that abciximab does not reduce in-stent restenosis. This supports Applicant's assertion that abciximab does not bind directly to Mac-1 or the response would be consistent between in-stent and balloon injured vessels. Applicants demonstrate in example 2 of the specification that a selective anti-Mac-1 antibody reduces both in-stent and balloon angioplasty injured restenosis.

The claimed method is not anticipated because Genetta does not disclose an antibody that ***specifically*** binds Mac-1, which ***specifically*** inhibits or reduces leukocyte integrin-mediated adhesion or function.

The further failure of the antibody of Genetta to anticipate the claims is shown by the attached articles by Dietch et al. (Arterioscler Thromb Vasc Biol 1998 18:1730-1737), and Simon et al (J Clin Invest 2000 105:293-300) which demonstrate that abciximab has no effect on restenosis. These papers support the ERASER study previously made of record.

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Claims 1-6, 8 and 10 were rejected under 35 U.S.C. § 102(b) as being anticipated by Simon et al., Circulation 92(8), 1-110 Abs 0519 (1995) "as evidenced by" Schwarz et al, Thromb Res 107,121-128 (2002), Bendeck et al, Wu et al and ERASER Investigators. Applicants respectfully traverse this rejection.

Simon et al (Circulation)

Simon, et al., (Circulation) reports on studies using an antibody fragment c7E3 immunoreactive with platelet glycoprotein IIb/IIa. Simon reports that the antibody was effective at reducing **"ischemic complications"** six months after coronary angioplasty and clinical restenosis. Simon also reports that the antibody is **cross-reactive** with Mac-1.

7E3 Antibody does not inhibit Restenosis.

The 7E3 antibody is known to inhibit integrin binding in cell culture, and be very effective in treating **thrombotic** conditions. However, treatment of thrombotic complications **(i.e., ischemia and ischemia-reperfusion injury)** is not the same as, nor predictive of, treatment of patients to prevent or reduce restenosis. The abstract does not report treatment of patients, the dosages, the times of administration nor indeed is that the focus of the abstract. The abstract reports *in vitro* studies that identify the activity of the antibody as cross-reactive with Mac-1 as well as platelet glycoprotein IIb/IIa. The patent describes treatment of a different class of patients, at different administration times and dosages, via its interaction with platelet glycoprotein IIb/IIa.

Thrombolysis causes injury due to a disruption in blood flow, followed by reperfusion, where the endothelium is intact. In contrast, restenosis is injury arising when there is disruption in the endothelium while the blood flow remains continuous. Restenosis involves recruitment of platelets and leukocytes.

As shown by the enclosed article, Mickelson, et al., "Chimeric 7E3 Fab (ReoPro) decreases detectable CD11b on neutrophils from patients undergoing coronary angioplasty", J. Am. Coll. Cardiol. 33(1):97-106 (1999), this antibody decreases detectable CD11b on neutrophils **but does not bind to neutrophils nor inhibit adhesion, two of the major factors involved in restenosis**. See also Deitch, et al., "Effects of beta3-integrin blockade (c7E3) on the response to angioplasty and intra-arterial stenting in atherosclerotic nonhuman primates", Arterioscler. Thromb. Vasc. Biol. 18(11):1730-7 (1998 Nov.) As further shown by the previously submitted paper, The Eraser Investigators, "Acute Platelet Inhibition with Abciximab Does Not Reduce In-Stent Restenosis (ERASER Study), Circulation 100:799-806 (1999), this antibody did not inhibit restenosis.

This evidence demonstrates that this antibody ("Reopro") does not specifically bind to a listed integrin, does not bind to neutrophils nor inhibit adhesion, nor ultimately, inhibit stenosis or restenosis, as required by the claimed language. Therefore Simon, et al., does not disclose the claimed method.

Claims 1-6, 8, 10-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,976,532 to Coller et al "as evidenced by" Schwarz et al. Thromb Res 107, 121-128

(2002), Bendeck et al, Wu et al and ERASER Investigations. Applicants respectfully traverse this rejection.

Coller et al

Coller et al., describes the 7E3 antibody which is discussed by Simon, et al., (Circulation). The patent reports that the antibody is specific for glycoprotein IIb/IIIa and can be used as an antithrombotic agent. There is no disclosure of the use of the antibody to inhibit or prevent restenosis; there is no disclosure that it binds to one of the listed integrins; nor is there any disclosure that it inhibits leukocyte-integrin mediated adhesion or function.

The secondary references cited to show the alleged "inherent Properties" of the antibody fail to make up for these deficiences. The legal standard for novelty is met.

Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,210,671 to Co et al. Applicants respectfully traverse this rejection.

Co et al.

Co describes the use of humanized immunoglobulins reactive with L-selectin. The examiner refers to col. 18, for use of the anti-L-selectin to treatment or prevention of ischemia-reperfusion injury.

Co does not teach administration of an effective amount of an antibody selectively binding to an integrin which inhibits or reduces lecukocyte-integrin mediated adhesion or function. Co teaches administration of an anti-L-selectin which can be administered with a second agent. This is not equivalent. The Examiner admits that Co et al. does not disclose the

claim limitations of stenosis and restenosis (page 27). Accordingly, Co fails to anticipate the claimed method since Co does not disclose an effective amount of a compound selectively binding to an integrin, to inhibit or reduce leukocyte-mediated adhesion or function. Co also fails to anticipate a method for inhibiting or reducing stenosis or restenosis as defined by the amended claims.

The examiner admits these differs on page 29 of the office action.

Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,935,234 to Todd et al.. Applicants respectfully traverse this rejection.

Todd et al.

Todd et al discloses methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocytic-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD 11b-.Mac-1- specific antibodies. The Examiner has admitted on page 28 of the Office Action that Todd does not disclose treating restenosis. Todd teaches administering antibodies to decrease the inflammatory response and infarct size, not decrease leukocyte-integrin mediated cell adhesion or function, as required by the claims. Todd teaches that occlusion causes myocardial infarct in an experimental canine model for myocardial infarct. As discussed above, myocardial infaction and ischemia are not the same as preventing stenosis or restenosis as claimed, nor can one extrapolate from studies with one to the other. Accordingly, Todd does not anticipate the claimed subject matter.

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Rejection Under 35 U.S.C. § 103

Claims 1-6, 8 and 10-12 were rejected under 35 U.S.C. § 103(a) as obvious over Co et al and/or Todd et al in combination with Simon et al., Mazzone et al, Circulation 88, 358-363 (1993), Ikeda et al. Am Heart J !28, 1091-1098 (1994), Inoue et al JACC 28,1127-1133 (1996) and Rogers et al, Circulation 88, 1215-1221 (1993). Applicants respectfully traverse these rejections.

a. The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest ***all elements of the claimed invention*** and the prior art does not suggest the modifications that would bring the primary references into conformity with the

application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992)(Emphasis added). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit recently warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit teachings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. WMS Gaming, Inc. v International Game Technology, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular." In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

b. The Prior Art

a. Co

Co is discussed above. Co does not teach using an effective amount of a single agent selectively inhibiting or reducing leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis after injury. Co relates to different compounds for different purposes.

b. *Todd, III, et al.*

Todd is discussed above. Todd also does not teach using an effective amount of a single agent selectively inhibiting or reducing leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis after injury. Todd relates to different compounds for different purposes.

c. Simon et al.

Simon is discussed above. Simon does not describe an antibody that selectively inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis after injury.

d. Mazonne

Mazonne does not disclose treating restenosis and does not disclose antibodies specific to Mac-1, much less using an effective amount of an antibody selectively inhibiting or reducing leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or restenosis after injury. Mazonne relates to treatment of unstable coronary artery

disease. Mazonne merely makes the observation that these patients have elevated expression of granulocyte and monocyte CD11b/CD18 adhesion receptors.

e. Ikeda

Ikeda discloses an increase in surface expression of CD11b after percutaneous transluminal coronary angioplasty ("PTCA"). Ikeda is an early study that shows that Mac-1 is one of several non-specific markers of leukocyte activation. No data has been shown that Mac-1 is involved in restenosis, much less any of the other claim elements, which are drawn to a method of treatment.

f. *Inoue*

Inoue does not teach an antibody specific to Mac-1. Inoue shows that leukocytes are activated by angioplasty to a greater degree in those that developed restenosis.

g. *Rogers*

Rogers describes the unsuccessful use of heparin to prevent restenosis.

h. *There is no motivation to combine the references*

Not only do these reference not disclose all of the claim elements, they fail to provide the motivation for one of skill in the art to modify and combine what is disclosed, as applicants have done. It has been made very clear that "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Further, the "level of skill in the art cannot be relied upon to provide the suggestion to

combine references. Al-site Corp v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication. In this case, there is no teaching in the prior art that would suggest combining the references, and the Applicants have also achieved unexpected results.

Efforts at limiting the undesirable proliferative and disease states of vascular endothelium have focused on the isolated administration of analogs of endothelial compounds. Certain drugs, such as heparin, are especially effective inhibitors of vascular smooth muscle cell proliferation in tissue culture and animal models of arterial diseases precisely because they mimic the activity of natural endothelial-derived compounds like heparan sulfate proteoglycan, Edelman, E.R. & Karnovskv, M.J. *Circ.* 89: 770-776 (1994). However, despite cell culture and small animal data supporting the regulatory role of heparin-like compounds, exogenous heparin preparations have shown no benefit in human trials. Non-heparin endothelial compounds such as nitric oxide and the prostaglandins are potent regulators of a range of biologic effects involving smooth muscle cells. Inhibitors of these compounds have been shown to control intimal hyperplasia following experimental vascular injury (Cooke et al., *Curr. Opin. Cardiol.*, 7: 799-804 (1992); Moncada et

al., *N. Engl. J. Med.*, *329*: 2002-2012 (1993); McNamara, et al., *Biochem. Biophys. Res. Comm.*, *193*: 291-296 (1993)). This is indicative that the vascular endothelium is a powerful regulator of the blood vessel wall, not because of the production and secretion of one compound alone, but because of its presence as an intact unit.

One skilled in the art would not expect only a single compound to be effective in limiting or preventing restenosis. This is demonstrated by Co et al. where antibodies are administered in combination with thrombolytic agents or angioplasty. The results obtained by applicants showing that a single class of compound, compounds blocking binding and activation of certain integrins, could effectively limit restenosis were completely unexpected. Importantly, it is not administration of a single compound, but class of compounds, that achieves this effect. These compounds inhibit or reduce leukocyte adhesion or function by interference with integrin-mediated binding.

Double Patenting Rejection

Claims 1-6, 8 and 10-12 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over U.S. Application Serial No. 09/776,533. Applicants will defer any discussion of this issue until resolution of the restriction and election of species requirements in the related case, and the patentability of the claims in this case.

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Allowance of claims 1-12 is respectfully solicited.

Respectfully submitted,

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Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, January 30, 2004 , to the Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

Jenny Vicente

Date: January 30, 2004

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Marked-up Copy of
Abstract of the Invention

Compounds that specifically inhibit or reduce leukocyte adhesion or function are useful to enhance vascular healing and lessen restenosis of blood vessels after revascularization, via angioplasty or bypass surgery, of diseased coronary, peripheral and cerebral arteries, and lessen stenosis or restenosis of surgically-placed bypass grafts and transplanted organs. Examples of these compounds are those which block cell surface integrins ~~or their ligands, for example, the leukocyte integrin~~ [such as] Mac-1 (CD11b/CD18, M2) [or their ligands]. ~~As demonstrated by the examples,~~ [B]~~both~~ superficial and deep injury was significantly reduced with treatment using an antibody to Mac-1 compared to both saline controls and IgG controls [in the examples]. After balloon angioplasty (superficial injury) neointimal area was reduced nearly 70%. The ratio of intimal:medial area~~, which is customarily used in balloon-injured experimental arteries to normalize for small normal variations in arterial size from one animal to another,~~ was reduced over 75%. After endovascular stent implantation (deep injury) neointimal area was reduced nearly 40%. Extrapolated to humans, this reduction in the intimal thickening would reduce [occurrence of] restenosis from ~~occurring in~~ approximately 30% of patients to less than 10% ~~of patients~~.